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ANNUAL PROGRESS REPORT

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September 1, 1962 through June 30, 1963

Principal Investigator:

John P. Merrill, M.D.
Associate Clinical Professor of Medicine, Harvard Medical School
Physician, Peter Bent Brigham Hospital

Title of Report:

Metabolic Disorders and Therapeutic Approaches to Renal Failure

Contract Number:

DA-49-007-MD-429

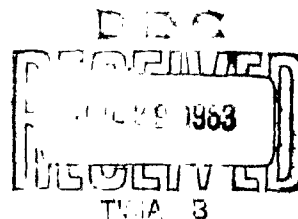
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A B S T R A C T

Preparing Institution:

Harvard Medical School and Peter Bent Brigham Hospital, Boston, Massachusetts

Title of Report: Metabolic Disorders and Therapeutic Approaches to Renal Failure

Principal Investigator: John P. Merrill, M.D.

Number of Pages: 3

Date: June 20, 1963

Contract Number: DA-49-007-MD-429

Supported By: U. S. Army Medical Research & Development Command
Department of the Army
Washington 25, D.C.

Descriptive Abstract:

1. A model system for determining skin histocompatibility in man has been described, based upon the acceleration of grafts on an indifferent recipient immunized previously by one member of the donor-recipient pair to be tested.
2. An alpha-1 glyco-protein isolated from the serum and concentrated in thymic tissue prolonged the life of 30% of homologous skin grafts in rats for 6 months.
3. Utilizing immunosuppressive therapy in the form of Imuran, Actinomycin-C, Azaserine and Cortisone we have produced prolonged tolerance for a human renal homograft from a nontwin donor in 5 recipients. In one of these a kidney transplanted from a cadaver has functioned well enough to sustain active life for 15 months.
4. An inlying plastic conduit for the performance of long-term, chronic peritoneal irrigation is described and has been utilized by two patients performing peritoneal dialysis at home for a period of 9 months. A device for the automatic cycling of the peritoneal fluid has been devised and is under test.
5. Homograft antigens on canine platelets have been isolated in soluble form. Homograft antibody elicited from rejected canine kidneys in a soluble fluid phase will react with this antigen in the classic immune reaction of agglutination, complement fixation and immune adherence.

Annual Progress Report -1-

In the course of our investigation of the problem of renal homografting in the human, we have extended the studies of other tissue homografts, particularly skin. Since the problem of skin grafting has particular pertinence for the military our progress in this area will be emphasized in this report. We have concluded a study of a model system for determining histocompatibility in man by the use of multiple skin grafts. This paper has been accepted for publication in the Journal of Clinical Investigation. (A Model System for Determining Histocompatibility in Man. Wilson, R.E., Henry, L. and Merrill, J.P.: J. Clin. Invest. In Press). In these studies donor and recipient pairs of several different combinations were chosen to explore the validity of such a model system. Full thickness skin grafts were placed. In a typical experiment skin was grafted from A to C. At the end of two weeks a second skin graft from B was placed on C. Full thickness biopsies of the first graft were taken between 7 and 14 days and the biopsy was always taken of the second graft on Day 6. If A and B were the same individual or were identical twins C would have been immunized by exposure to the first graft and therefore the second graft would be rejected in an accelerated fashion; in this instance in the most accelerated fashion, represented by a "white graft". If A and B were different individuals but had some antigenic similarity, the second skin graft would be rejected in an accelerated fashion and if they had little antigenic resemblance C would behave upon receiving a graft from B as though he had never been exposed to B's antigen. This graft, then, would be rejected as a "first set" graft. Twenty pairs of skin grafts were done in all. All pairs of identical twins produced white grafts as predicted. In none of 3 pairs of nonidentical twins was there acceleration of the second graft in an indifferent recipient. A high degree of cross re-activity in the heterogenous human population was found. The ability to predict this relationship constitutes a beginning of a tissue typing assay based upon the skin grafting in which the biologic activity of the test

system is more closely related to the basic problem of transplantation than are blood iso-agglutinins or leuco-agglutinins.

Doctor James Mowbray of St. Mary's Hospital, London has for the past year continued in our laboratory work done by him in England. Doctor Mowbray has isolated from the serum, and more recently from thymic tissue, an alpha-1 glycoprotein which, injected into rats, will prolong the life of 30% of homologous skin grafts beyond 6 months. This protein has been shown to have RNase activity as well as phosphatase activity and has a distinctive band on paper electrophoresis. Doctor Mowbray has shown that this band disappears from the blood of thymectomized dogs. Preliminary evidence obtained in the last month suggests that he may have crystallized this substance, thus making its further study more precise.

We have studied the effect of antimetabolites and cortisone upon the prolongation of human skin grafts. Six patients with glomerulonephritis and/or lupus erythematosus have had unrelated skin homografts placed shortly before the beginning of antimetabolite therapy for their renal lesion. Prolongation of the skin graft has been shown in 5 of 6 cases, in one instance to longer than one month. Discontinuance of the antimetabolite therapy results in rapid rejection of the skin graft within a period of 48 hours.

Work has continued with human renal homografts utilizing immunosuppressive therapy in the form of Imuran (azathiopurine), actinomycin-C, azaserine and cortisone. At the present time, two recipients who have received renal homografts from mother to son are alive and well at 1 and 6 months. One recipient who received a homograft from his brother is alive and well at 6 months and one recipient of an unrelated cadaver kidney is alive and well, although with diminished renal function, at 15 months. The results of these studies have been summarized in a recent publication (Murray, J.E., Merrill, J.P., Harrison, J. H., Wilson, R. E., and Damm, G.J.: Prolonged survival of human-kidney homografts by immunosuppressive drug therapy. New Eng. J. Med. 268:1315, June, 1963) and a study of the course of the recipient of a cadaver kidney will be published in detail in the near future.

Chernoff, J., Murray, J.E., Merrill, J.P., Harrison, J.H., Wilson, R.E., and Damm, G.J.

Dammin, G.J.: Successful transplantation of kidney from a human cadaver. J. A. M.A. In Press).

In all of these cases, prolonged partial tolerance to the kidney has occurred and a number of episodes of incipient rejection of the renal homograft have been reversed by the use of actinomycin-C and cortisone.

We have continued our work with peritoneal irrigation utilizing an indwelling plastic conduit through which access may be gained into the peritoneal cavity for long-term maintenance of the uremic patient. Two such patients have been maintained for periods of 9 months and several for lesser periods. In 4 of these individuals peritoneal irrigation was performed at home by another member of the household. We have recently devised and tested an apparatus for the automatic cycling of the peritoneal fluid so that dialysis may be performed at home while the patient sleeps.

Experimental work done in 1961 and 1962 has demonstrated the presence of homograft antigens on canine platelets. Further studies have shown that this material can be removed from the platelet in soluble form which can be further characterized by column chromatography. In an effort to supplement the in vivo biologic test for the presence of antigen, we have demonstrated that antibody can be eluded from its usual cell-bound state (in the rejecting homograft) into a soluble fluid phase. As such it may act in the classic immune reactions of agglutination, complement fixation and immune adherence. The work in this area thus has now progressed to the point where we have available soluble homograft antigen and soluble homograft antibody which react with one another in the fashion predicted by classical immunologic experience.

A B S T R A C T

Preparing Institution:

Harvard Medical School and Peter Bent Brigham Hospital, Boston, Massachusetts

Title of Report: Metabolic Disorders and Therapeutic Approaches to Renal Failure

Principal Investigator: John P. Merrill, M.D.

Number of Pages: 3

Date: June 20, 1963

Contract Number: DA-49-007-MC-128

Supported By: U. S. Army Medical Research & Development Command
Department of the Army
Washington 25, D.C.

Descriptive Abstract.

1. A model system for determining skin histocompatibility in man has been described, based upon the acceleration of grafts on an indifferent recipient immobilized previously by one member of the donor-recipient pair to be tested.

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4. An indyling plastic conduit for the performance of long-term, chronic peritoneal irrigation is described and has been utilized by two patients performing peritoneal dialysis at home for a period of 9 months. A device for the automatic cycling of the peritoneal fluid has been devised and is under test.

5. Homograft antigens on canine platelets have been isolated in soluble form. Homograft antibody elicited from rejected canine kidneys in a soluble fluid phase will react with this antigen in the classical immune reaction of agglutination.

6. A method for the isolation and characterization of platelets from canine blood is described.

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